Prevalence of myocardial fibrosis among patients living with HIV and factors associated with a higher prevalence rate: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction HIV infection is an established risk factor for the development of cardiovascular diseases. Although increasing evidence implicates a higher prevalence of myocardial fibrosis (MF) among patients living with HIV (PLWH) compared with the HIV-negative population, there is a paucity of knowledge regarding its determinants and factors associated with higher odds of MF development. We aim to perform a systematic review to estimate the prevalence of MF among PLWH. Additionally, we will determine the factors associated with higher odds of MF among PLWH compared with the HIV-negative population.

Methods A systematic review will be performed by consulting the Cochrane handbook for systematic reviews of interventional studies reporting a confirmed diagnosis of MF among PLWH. Articles will be eligible if they provide the prevalence of MF among PLWH and HIV-negative populations or the odds ratio (OR) and 95% confidence interval (CI) of MF development in relation to HIV. Depending on the quality of the data and the heterogeneity among the included studies, a random-effects or fixed-effects model will be used to pool and compare the ORs of MF among PLWH and HIV-negative population. Factors associated with higher odds of MF in relation to HIV will also be determined.

Ethics and dissemination Ethical approval and obtaining informed consent are not required for this systematic review as it does not use individual patients’ data. Results of this study will be published in a peer-reviewed medical journal.

INTRODUCTION

Infection with HIV is a risk factor for the development of coronary artery disease, heart failure, arrhythmia and ischaemic stroke. Additionally, the prevalence of cardiac abnormalities is reportedly higher in patients living with HIV (PLWH) than in the normal population. Postmortem studies have indicated a higher prevalence of cardiomyopathy and myocardial fibrosis (MF) among PLWH than among the HIV-negative population. Although the higher rate of cardiovascular diseases among PLWH has been contributed to a higher prevalence of traditional risk factors and metabolic derangements, the relative risk remains significant after adjusting for these covariates and considering the use of modern antiretroviral therapy (ART) with fewer metabolic adverse effects.

MF is reportedly a prevalent finding in postmortem studies of patients with sudden cardiac death (SCD). However, the majority of patients with SCD who are found to have MF were asymptomatic or showed nonspecific symptoms before death. Emerging evidence indicates that subclinical myocardial inflammation and fibrosis are prevalent findings among PLWH.

Aim As MF substantially increases the risk of SCD along with other clinically significant electrocardiographic abnormalities, we aimed to perform a systematic review of the published literature to estimate the prevalence of developing MF in relation to HIV and identify factors associated with a higher prevalence rate among PLWH.
Rationale

PLWH are reportedly predisposed to coronary artery and other atherosclerotic cardiovascular diseases. Additionally, radiological and histological studies have shown a higher detection rate for MF among PLWH than among HIV-negative population. As the risk of SCD increases with the existence and extent of MF among PLWH and their HIV-negative counterparts, a systematic review of the literature is needed to quantify this risk.

METHODS

Study design

A systematic review will be conducted by consulting the Cochrane handbook for systematic reviews of interventions and will be reported according to the preferred reporting checklist for meta-analysis of observational studies in epidemiology. We aim to identify human studies in the English language that provide original data on PLWH who have been diagnosed with MF (online supplemental file 1). Original data will be defined as no synthesis of literature data or reanalysis of previously published results. The protocol for this systematic review has been registered with the Open Science Framework with the following digital object identifier (DOI): 10.17605/OSF.IO/7UPBK.

Review questions

What is the prevalence of MF among PLWH and what factors increase the odds of MF among PLWH compared with HIV-negative population? The review questions have been specified further in online supplemental file 1.

Search strategy

Two investigators will independently review the literature available online in the following databases: MEDLINE/PubMed, EMBASE/Ovid, Web of Science and Google Scholar from inception to 31 December 2022. A combination of the following search terms reflecting the review questions will be used: “cardiac fibrosis”, “myocardial fibrosis”, “endomyocardial fibrosis” and “HIV” or “human immunodeficiency virus”. The precise search strategy is presented in online supplemental file 2 for MEDLINE/PubMed. This strategy will be modified for each other databases by consulting an experienced librarian with expertise in biomedical literature review.

The bibliography of relevant articles and key journals in the fields of HIV, infectious diseases, cardiology, cardiovascular diseases and radiology will be manually searched to identify additional literature. Owing to the uncertainty of the quality of grey literature, it will not be taken into consideration in this systematic review.

The titles and abstracts of the articles retrieved through these searches will be screened for their relevance. Thereafter, the full text of the relevant articles will be retrieved to ensure eligibility. Any discrepancies in the selection of studies will be resolved by discussion with a senior investigator.

Study eligibility

Studies will be included in this systematic review if they meet all the following inclusion criteria:

1. Full text is accessible in English language.
2. Original data on adults (age ≥18 years) with HIV (PLWH) is provided.
3. A diagnosis of MF has been established in the study participants using a universally accepted diagnostic modality, such as cardiac MRI or biopsy.
4. The frequency of MF among PLWH and HIV-negative population, or the odds ratio (OR) and 95% confidence interval (CI) of developing MF in relation to HIV has been provided.

Studies will be excluded if they meet any of the following exclusion criteria:

1. Original data on the concept of MF among PLWH is not provided; the paper is a review article or reanalysis of previously published datasets; and editorial or commentaries without any original data.
2. Diagnosis of HIV infection or MF is a presumption and has not been confirmed based on the standard-of-care diagnostic modality.
3. Full text is not available or cannot be obtained in English language.
4. Case reports or single-arm studies with inherent methodological limitations in estimating the OR for the development of MF among PLWH.

**Data extraction**

After full texts of the eligible studies have been obtained and stored in a shared drive, two investigators will read and extract data from these articles. Data on the variables of interest will be entered into a predesigned online spreadsheet for further evaluation. A third investigator will oversee the data extraction process to ensure accuracy and consistency. In case of missing data, an attempt will be made to contact the senior author of the study in question.

The following data will be collected: patients’ demographics (age, sex and race/ethnicity), socioeconomic status (educational level, household income, and geographic region), medical conditions (comorbidities, coexisting clinical conditions, prescribed medications, antiretroviral therapy [ART] regimen, environmental and/or occupational exposures, nutritional status and lifestyle features), features of MF (time from diagnosis of HIV to the diagnosis of MF, time from initiation or latest change of ART to the diagnosis of MF, diagnostic modality for MF, histological studies if available and other cardiovascular diagnostic information).

**Quality assessment**

The quality of the included studies will be assessed at the time of data extraction by two independent investigators, using the Newcastle-Ottawa Scale and mixed-methods appraisal tools. These quality assessment tools are appropriate for the nature of the studies, which primarily comprises non-randomised and observational studies. Although no study will be excluded from this systematic review based on quality assessment, the quality score will be reflected in the results of the data synthesis.

**Meta-analysis**

The extracted data will be curated for narrative synthesis and qualitative appraisal by the senior author. If sufficient data are available on the frequency of MF among PLWH and HIV-negative population, a meta-regression analysis will be conducted after adjusting for confounders, such as ART, to determine the OR and 95% CI of MF in relation to HIV. Furthermore, factors associated with higher odds of MF will be compared between those who developed the condition and those who did not among PLWH. If the OR for developing MF has been provided, a meta-analysis will be performed to estimate the pooled OR and 95% CI, using either a random-effects model for high-heterogeneity data or a fixed-effects model for medium-to-low heterogeneity data. Statistical heterogeneity among studies will be assessed using the $I^2$ statistic. $I^2 <30\%$, 30% < $I^2$ < 60 and $I^2 > 60\%$ will be classified as low, medium and high heterogeneity, respectively.

**Subgroup analysis**

The included studies will have used different diagnostic modalities to diagnose MF. Hence, we will attempt to stratify the patient population based on diagnostic modalities to avoid any potential bias in the estimated odds ratio of MF development among PLWH compared with HIV-negative patients.

**Statistical tools**

Statistical analyses will be performed using STATA (V.16; StataCorp). Results will be considered statistically significant when the OR and 95% CIs does not include the null value of 1 or the p value is <0.05. Forest plots will be used to visualise the results of the meta-analysis on the estimated pooled ORs and 95% CIs. If more than 10 studies are available, a funnel plot will be constructed to demonstrate potential publication bias.

**Patient and public involvement**

No patients will be directly involved in this study.

**Discussion**

A significantly higher prevalence of cardiac diseases is seen among PLWH than among the HIV-negative population. However, the clinical outcomes associated with HIV-related cardiomyopathy vary based on the extent of cardiac involvement. Moreover, the underlying mechanisms through which HIV affects the heart remain largely unexplained.

In a comparative observational study of 47 HIV-positive and 21 HIV-negative individuals, Yan et al evaluated myocardial structure and function using a comprehensive, multiparametric, cardiac MR (CMR) scan protocol. PLWH had significantly lower left and right systolic functions than did HIV-negative controls. Additionally, late gadolinium enhancement suggestive of MF was detected in 21.95% of HIV-negative patients, compared with none in HIV-negative patients. Factors associated with higher odds of MF development, as detected on CMR, included progression to AIDS (OR: 6.3), HIV duration > 5 years (OR: 4.3), age > 40 years (OR: 2.4), CD4+ cell count < 500 cells/mm$^3$ (OR: 1.84) and viral load (plasma HIV RNA) > 75 copies/mL (OR: 1.6). Another study by Tseng et al used post-mortem data of 108 PLWH who had out-of-hospital cardiac arrests (61 non-SCDs and 47 SCDs) and found a significantly higher fibrosis burden (mean percent fibrosis) in the interstitial myocardium and perivascular tissue of PLWH than in HIV-negative patients. Although the proportion of arrhythmia-induced SCD was similar between the HIV-positive and HIV-negative patients (47% vs 56%), drug overdose was significantly higher among PLWH (34% vs 13%). This suggests that although chronic inflammation in HIV infection...
might provide a susceptible environment for fibrosis development, major cardiovascular events arise due to other behavioural and metabolic risk factors.

Many studies on PLWH who present with cardiovascular events have a retrospective design, small sample size and lack comprehensive data on the underlying mechanisms for the development of different cardiovascular manifestations. This systematic review aims to narrow the knowledge gap between HIV diagnosis and accelerated occurrence of cardiovascular diseases, specifically MF. Additionally, MF is most likely underreported in the literature among PLWH and HIV-negative individuals. However, we expect that the OR of developing MF is proportionally affected by this under-reporting.

Ethics and dissemination
Ethical approval and obtaining an informed consent are not required for this systematic review as it does not use identifiable data of individual patients. Results of this study will be published in a peer-reviewed medical journal.

Contributors SS: study design, literature review, drafting of the manuscript, final revision of the manuscript for intellectual changes. CDD: literature review, drafting of the manuscript, final revision of the manuscript for intellectual changes. NMH: literature review, drafting of the manuscript, final revision of the manuscript for intellectual changes. CDD: literature review, drafting of the manuscript, final revision of the manuscript for intellectual changes. NS: study design, literature review, final revision of the manuscript for intellectual changes.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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